10/805,885

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
RELATED PATENTS L1	1	("6602875").PN.	USPAT	OR	OFF	2006/04/18 08:36
L2	1	("6660740").PN.	USPAT	OR	OFF	2006/04/18 08:36
L3	1	("6809099").PN.	USPAT	OR	OFF	2006/04/18 08:37
L4	218	544/346	USPAT	OR	OFF	2006/04/18 08:38
L5	246	544/346	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2006/04/18 08:38
L6	6	l5 and (gsk or (glycogen adj synthase) or [1,2,4]triazolo[4, 3-a]quinoxaline or [1,2,4]triazolo[3, 4-a]quinoxaline)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2006/04/18 08:39

*STN SEARCH TRANSCRIPT FOR 10/805,885

```
Connecting via Winsock to STN


Welcome to STN International!  Enter x:x

LOGINID:SSSPTA1623ZCT

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *     Welcome to STN International     * * * * * * * * * *

 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  DEC 23  New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/
                  USPAT2
 NEWS  4  JAN 13  IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
 NEWS  5  JAN 13  New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to
                  INPADOC
 NEWS  6  JAN 17  Pre-1988 INPI data added to MARPAT
 NEWS  7  JAN 17  IPC 8 in the WPI family of databases including WPIFV
 NEWS  8  JAN 30  Saved answer limit increased
 NEWS  9  FEB 21  STN AnaVist, Version 1.1, lets you share your STN AnaVist
                  visualization results
 NEWS 10  FEB 22  The IPC thesaurus added to additional patent databases on STN
 NEWS 11  FEB 22  Updates in EPFULL; IPC 8 enhancements added
 NEWS 12  FEB 27  New STN AnaVist pricing effective March 1, 2006
 NEWS 13  FEB 28  MEDLINE/LMEDLINE reload improves functionality
 NEWS 14  FEB 28  TOXCENTER reloaded with enhancements
 NEWS 15  FEB 28  REGISTRY/ZREGISTRY enhanced with more experimental spectral
                  property data
 NEWS 16  MAR 01  INSPEC reloaded and enhanced
 NEWS 17  MAR 03  Updates in PATDPA; addition of IPC 8 data without attributes
 NEWS 18  MAR 08  X.25 communication option no longer available after June 2006
 NEWS 19  MAR 22  EMBASE is now updated on a daily basis
 NEWS 20  APR 03  New IPC 8 fields and IPC thesaurus added to PATDPAFULL
 NEWS 21  APR 03  Bibliographic data updates resume; new IPC 8 fields and IPC
                  thesaurus added in PCTFULL
 NEWS 22  APR 04  STN AnaVist $500 visualization usage credit offered
 NEWS 23  APR 12  LINSPEC, learning database for INSPEC, reloaded and enhanced
 NEWS 24  APR 12  Improved structure highlighting in FQHIT and QHIT display
                  in MARPAT
 NEWS 25  APR 12  Derwent World Patents Index to be reloaded and enhanced during
                  second quarter; strategies may be affected

 NEWS EXPRESS  FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a,
               CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
               V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT
               http://download.cas.org/express/v8.0-Discover/

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS LOGIN    Welcome Banner and News Items
 NEWS IPC8     For general information regarding STN implementation of IPC 8

Enter NEWS followed by the item number or name to see news on that
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* * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 08:53:24 ON 18 APR 2006

=> file reg
COST IN U.S. DOLLARS                              SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'REGISTRY' ENTERED AT 08:53:30 ON 18 APR 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 American Chemical Society (ACS)

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STRUCTURE FILE UPDATES:    17 APR 2006  HIGHEST RN 880759-42-2
DICTIONARY FILE UPDATES:   17 APR 2006  HIGHEST RN 880759-42-2

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

*******************************************************************
*                                                                 *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,  *
* effective March 20, 2005.  A new display format, IDERL, is now   *
* available and contains the CA role and document type information. *
*                                                                 *
*******************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> ....Testing the current file.... screen

ENTER SCREEN EXPRESSION OR (END):end


=>
Uploading C:\Program Files\Stnexp\Queries\TRIAZOLOQUINOXALINE GSK INHs.str
```
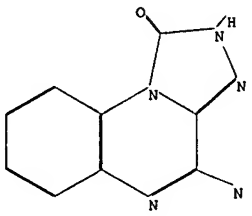
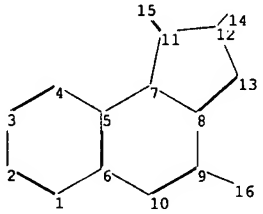





chain nodes :
14 15
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13
ring/chain nodes :
16
chain bonds :
9-16 11-15 12-14
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 7-11 8-9 8-13 9-10 11-12 12-13
exact/norm bonds :
5-7 6-10 7-8 7-11 8-9 8-13 9-10 9-16 11-12 11-15 12-13
exact bonds :
12-14
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6

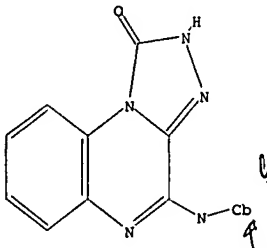
Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:CLASS 15:CLASS 16:CLASS

L1 STRUCTURE UPLOADED

=> que L1

L2 QUE L1

=> d l1
L1 HAS NO ANSWERS
L1 STR



ELECTED SP.
(IS CYCLOHEXANE)

SATURATED, CARBOCYCLIC

Structure attributes must be viewed using STN Express query preparation.

=> s l1
SAMPLE SEARCH INITIATED 08:54:05 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 24 TO ITERATE

100.0% PROCESSED 24 ITERATIONS 1 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 187 TO 773
PROJECTED ANSWERS: 1 TO 80

L3 1 SEA SSS SAM L1

=> file caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 0.44 0.65

FILE 'CAPLUS' ENTERED AT 08:54:11 ON 18 APR 2006
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FILE COVERS 1907 - 18 Apr 2006 VOL 144 ISS 17
FILE LAST UPDATED: 17 Apr 2006 (20060417/ED)

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=> file reg
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 1.38 2.03

FILE 'REGISTRY' ENTERED AT 08:55:41 ON 18 APR 2006
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STRUCTURE FILE UPDATES: 17 APR 2006 HIGHEST RN 880759-42-2
DICTIONARY FILE UPDATES: 17 APR 2006 HIGHEST RN 880759-42-2

New CAS Information Use Policies, enter HELP USAGETERMS for details.

```
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  conducting SmartSELECT searches.

**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information.  *
*                                                                    *
**********************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> s l1 sss full
FULL SEARCH INITIATED 08:55:45 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      521 TO ITERATE

100.0% PROCESSED      521 ITERATIONS                          1 ANSWERS
SEARCH TIME: 00.00.01

L4            1 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY   SESSION
FULL ESTIMATED COST                             166.94    168.97

FILE 'CAPLUS' ENTERED AT 08:55:50 ON 18 APR 2006
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FILE LAST UPDATED: 17 Apr 2006  (20060417/ED)

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=> s l4
L5            1 L4
```

```
=> d

L5   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2006 ACS on STN
AN   2004:802563  CAPLUS
DN   141:314348
TI   Preparation of substituted 4-amino[1,2,4]triazolo[4,3-a]quinoxalines for
     treating glycogen synthase kinase 3 (GSK-3) mediated conditions
IN   Benbow, John W.; Chu-Moyer, Margaret Y.; Kung, Daniel W.
PA   Pfizer Inc., USA
SO   U.S. Pat. Appl. Publ., 27 pp.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.          DATE
     --------------      ----   --------    -------------------      --------
PI   US 2004192698       A1     20040930    US 2004-805985           20040322
     CA 2520251          AA     20041007    CA 2004-2520251          20040315
     WO 2004085439       A1     20041007    WO 2004-IB835            20040315
          W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
              CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
              GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
              LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
              NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
              TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
          RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
              BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,
              ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
              SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,
              TD, TG
     EP 1613629          A1     20060111    EP 2004-720674           20040315
          R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
              IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK
     BR 2004007926       A      20060221    BR 2004-7926             20040315
PRAI US 2003-458500P     P      20030327
     WO 2004-IB835       W      20040315
OS   MARPAT 141:314348
```

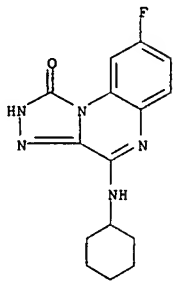
APPLICANTS

```
=> d hitstr

L5   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2006 ACS on STN
IT   766543-65-1P
     RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
     (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
     (Uses)
        (preparation of substituted 4-amino[1,2,4]triazolo[4,3-a]quinoxalines for
        treating glycogen synthase kinase 3 (GSK-3) mediated conditions)
RN   766543-65-1  CAPLUS
CN   [1,2,4]Triazolo[4,3-a]quinoxalin-1(2H)-one, 4-(cyclohexylamino)-8-fluoro-
     (9CI)  (CA INDEX NAME)
```

ONLY 1 HIT W/ N-SATURATED-CARBOCYCLIC

SEARCH.



ELECTED SP.

=> THIS COMPOUND ^ IS THE ELECTED SPECIES
THIS IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> OK, BACK TO REGISTRY, BROADEN SEARCH TO Ra AND Rb ARE = TO ANYTHING.
OK, IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> FILE REG

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	4.43	173.40

FILE 'REGISTRY' ENTERED AT 08:57:11 ON 18 APR 2006
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DICTIONARY FILE UPDATES: 17 APR 2006 HIGHEST RN 880759-42-2

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conducting SmartSELECT searches.

```
**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from  *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information.  *
*                                                                    *
**********************************************************************
```

Structure search iteration limits have been increased. See HELP SLIMITS
for details.

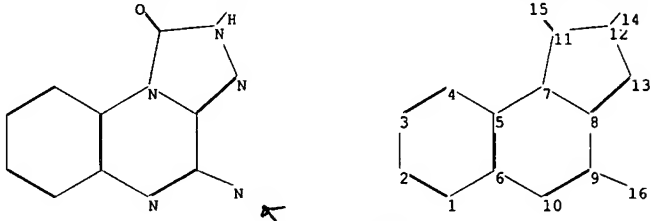
REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> ....Testing the current file.... screen

ENTER SCREEN EXPRESSION OR (END):end

=>
Uploading C:\Program Files\Stnexp\Queries\TRIAZOLOQUINOXALINE GSK INHs.str



ANYTHING CAN BE HERE NOW

chain nodes :
14 15
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13
ring/chain nodes :
16
chain bonds :
9-16 11-15 12-14
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-7 6-10 7-8 7-11 8-9 8-13 9-10 11-12 12-13
exact/norm bonds :
5-7 6-10 7-8 7-11 8-9 8-13 9-10 9-16 11-12 11-15 12-13
exact bonds :
12-14
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6

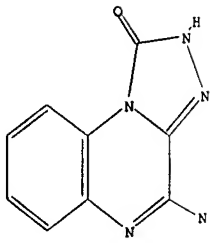
Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:CLASS 15:CLASS 16:CLASS

L6 STRUCTURE UPLOADED

=> que L6

L7 QUE L6

=> D L6
L6 HAS NO ANSWERS
L6 STR



Structure attributes must be viewed using STN Express query preparation.

=> S L6
SAMPLE SEARCH INITIATED 08:57:59 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 24 TO ITERATE

100.0% PROCESSED 24 ITERATIONS 6 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 187 TO 773
PROJECTED ANSWERS: 6 TO 266

L8 6 SEA SSS SAM L6

=> S L6 SSS FULL
FULL SEARCH INITIATED 09:00:30 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 521 TO ITERATE

100.0% PROCESSED 521 ITERATIONS 141 ANSWERS
SEARCH TIME: 00.00.01

L9 141 SEA SSS FUL L6

=> FILE CAPLUS
COST IN U.S. DOLLARS SINCE FILE ENTRY 169.14 TOTAL SESSION 342.54

FULL ESTIMATED COST

FILE 'CAPLUS' ENTERED AT 09:00:34 ON 18 APR 2006
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FILE LAST UPDATED: 17 Apr 2006 (20060417/ED)

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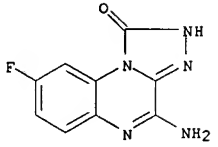
=> S L9 NOT L5
5 L9
L10 4 L9 NOT L5

*ALL COMPOUNDS HIT IN THIS SEARCH ARE EXCLUDED BY CL. 1 PROVISO.

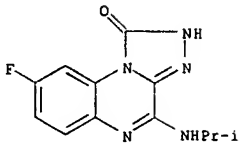
=> D 1-4 IBIB ABS HITSTR

L10 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:424662 CAPLUS
DOCUMENT NUMBER: 141:16902
TITLE: Models for the prediction of adenosine receptors binding activity of 4-amino[1,2,4]triazolo[4,3-a]quinoxalines
AUTHOR(S): Lather, V.; Madan, A. K.
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, Maharishi Dayanand University, Rohtak, 124001, India
SOURCE: THEOCHEM (2004), 678(1-3), 1-9
CODEN: THEODJ; ISSN: 0166-1280
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Relationship between the topol. indexes and the adenosine receptors (A1 and A2) binding activities of 4-amino[1,2,4]triazolo[4,3-a]quinoxalines, adenosine receptor antagonists has been investigated. Three topol. indexes, Wiener's Index-a distance based topol. descriptor, Zagreb group parameter-an adjacency-based topol. descriptor and eccentric connectivity index-an adjacency-cum-distance based topol. descriptor were used for the present investigations. A data set comprising of 138 analogs of 4-amino[1,2,4]triazolo[4,3-a]quinoxaline was selected for the present studies. The values of the Wiener's index, Zagreb group parameter and eccentric connectivity index for each of the 138 compds. comprising the data set were computed and suitable models developed after identification of active ranges. Subsequently, a biol. activity was assigned to each compound using these models, in the data set, which was then compared with the reported adenosine receptors (A1 and A2) binding activities. Accuracy of prediction using these models was found to vary from a min. of .apprx.80% to a maximum of .apprx.90%.
IT **127710-85-4 127710-87-6**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(models for prediction of adenosine receptors binding activity of aminotriazoloquinoxalines)
RN 127710-85-4 CAPLUS
CN [1,2,4]Triazolo[4,3-a]quinoxalin-1(2H)-one, 4-amino-8-fluoro- (9CI) (CA INDEX NAME)



RN 127710-87-6 CAPLUS

CN [1,2,4]Triazolo[4,3-a]quinoxalin-1(2H)-one, 8-fluoro-4-[(1-methylethyl)amino]- (9CI) (CA INDEX NAME)



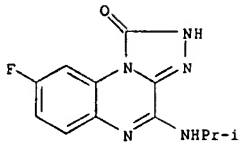
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:478038 CAPLUS
DOCUMENT NUMBER: 127:156859
TITLE: Interest of cluster significance analysis in structure-affinity relationships for non-xanthine heterocyclic antagonists of adenosine
AUTHOR(S): Adenot, M.; Benezech, V.; Bompart, J.; Bonnet, P. A.; Chapat, J. P.; Grassy, G.
CORPORATE SOURCE: Centre de Biochimie Structurale, UMR CNRS 9955, INSERM U414, Faculte de Pharmacie, Montpellier, 34060, Fr.
SOURCE: European Journal of Medicinal Chemistry (1997), 32(6), 493-504
CODEN: EJMCA5; ISSN: 0223-5234
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To define some predictive rules for the discrimination of adenosine antagonists by their A1-receptor affinity, the authors performed a systematic QSAR anal. As no significant descriptors of affinity were found, the authors then proposed to introduce a calculated enthalpy or entropy change for the interaction as a first approximation of the affinity descriptors. Since the structural details of the common receptor binding site remain to be determined, an indirect strategy was utilized involving the simulation of amino acid residues that are thought to interact with the ligand. Estimating enthalpic and entropic components by means of a semi-empirical quantum mech. AM1 force calcn., the authors found a significant clustering of enthalpy change values. This method provides a good descriptor of interaction and also a simple tool for testing hypotheses on the nature of putative binding sites.

IT **127710-87-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cluster significance anal. in structure-affinity relationships for non-xanthine heterocyclic antagonists of adenosine)

RN 127710-87-6 CAPLUS
CN [1,2,4]Triazolo[4,3-a]quinoxalin-1(2H)-one, 8-fluoro-4-[(1-methylethyl)amino]- (9CI) (CA INDEX NAME)



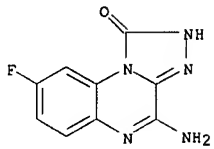
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:521646 CAPLUS
DOCUMENT NUMBER: 125:211825
TITLE: Fujita-Ban and Hansch analyses of A1- and A2-adenosine receptor binding affinities of some 4-amino[1,2,4]triazolo[4,3-a]quinoxalines
AUTHOR(S): Singh, P.; Ojha, T. N.; Tiwari, S.; Sharma, R. C.
CORPORATE SOURCE: Dep. of Chemistry, S K Government College, Sikar, 332 001, India
SOURCE: Indian Journal of Chemistry, Section B: Organic Chemistry Including Medicinal Chemistry (1996), 35B(9), 929-934
CODEN: IJSBDB; ISSN: 0376-4699
PUBLISHER: Publications & Information Directorate, CSIR
DOCUMENT TYPE: Journal
LANGUAGE: English

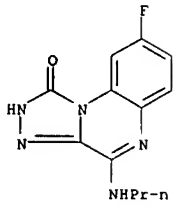
AB Both the Fujita-Ban and Hansch quant. structure-activity relation (QSAR) analyses have been attempted on the same data set, 4-amino[1,2,4]triazolo[4,3-a]quinoxalines as adenosine agonist ligands. The analyses have helped to ascertain the role of different substituents, X, Y and Z, resp., in the 1-, 4- and 7-/8-positions of the rigid tricyclic ring system in explaining the observed binding affinities. From both analyses for A1-receptor binding affinity, it is concluded that a substituent having a neg. Es-value (such as CF3) at X is more favorable than when X is Ph or when there is no substitution (X = H). Likewise, at Y a substitutional pattern of the type NHEt or NHiPr having a neg. field-effect imparts more potency than when the field-effect value is pos. At Z, a chloro substituent appears to cause better ligand binding than fluoro or no substitution. For A1-affinity, the substitutional requirements at X and Z have been predicted to be similar to those for A1-affinity. The nature of interaction of the X substituent is dissimilar at both A1- and A2-receptors. However, this WSAR anal. does not provide any clearcut selectivity criterion for the two receptor subtypes.

IT **127710-85-4 181484-70-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(analyses of A1- and A2-adenosine receptor binding affinities of aminotriazoloquinoxalines)

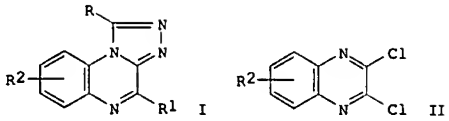
RN 127710-85-4 CAPLUS
CN [1,2,4]Triazolo[4,3-a]quinoxalin-1(2H)-one, 4-amino-8-fluoro- (9CI) (CA INDEX NAME)



RN 181484-70-8 CAPLUS
CN [1,2,4]Triazolo[4,3-a]quinoxalin-1(2H)-one, 8-fluoro-4-(propylamino)- (9CI) (CA INDEX NAME)



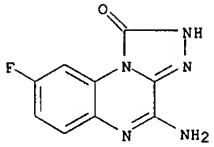
L10 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1990:459110 CAPLUS
DOCUMENT NUMBER: 113:59110
TITLE: 4-Amino[1,2,4]triazolo[4,3-a]quinoxalines. A novel class of potent adenosine receptor antagonists and potential rapid-onset antidepressants
AUTHOR(S): Sarges, Reinhard; Howard, Harry R.; Browne, Ronald G.; Lebel, Lorraine A.; Seymour, Patricia A.; Koe, B. Kenneth
CORPORATE SOURCE: Pfizer Cent. Res., Pfizer Inc., Groton, CT, 06340, USA
SOURCE: Journal of Medicinal Chemistry (1990), 33(8), 2240-54
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 113:59110
GI



AB A series of 4-amino[1,2,4]triazolo[4,3-a]quinoxalines (I; R = H, alkyl, OMe, etc.; R1 = amino; R2 = H, F, Cl, OMe) have been prepared from 2,3-dichloroquinoxaline II (same R2). E.g., treating II with NH2NH2, followed by cyclization with ortho esters RC(OR3)3 (same R; R3 = alkyl), and subsequent amination, gave I. Many compds. from this class reduce immobility in Porsolt's behavioral despair model in rats upon acute administration and may therefore have therapeutic potential as novel and rapid acting antidepressant agents. Optimal activity in this test is associated with hydrogen, CF3, or small alkyl groups in the 1-position, with NH2, NH-acetyl, or amines substituted with small alkyl groups in the 4-position, and with hydrogen or 8-halo substituents in the aromatic ring. Furthermore, many I bind avidly, and in some cases very selectively, to adenosine A1 and A2 receptors. A1 affinity of these compds. was measured by their inhibition of tritiated CHA (N6-cyclohexyladenosine) binding in rat cerebral cortex membranes and A2 affinity by their inhibition of tritiated NECA [5'-(N-ethylcarbamoyladenosine] binding to rat striatal homogenate in the presence of cold N6-cyclopentyladenosine. Structure-activity relationship studies show that best A1 affinity is associated with Et, CF3, or C2F5 in the 1-position, NHCHMe2 or NH-cycloalkyl in the 4-position, and with an 8-chloro substituent. Affinity at the A2 receptor is mostly dependent on the presence of an NH2 group in the 4-position and is enhanced by Ph, CF3, or Et in the 1-position. The most selective A1 ligand by a factor of >3000 is 8-chloro-4-(cyclohexylamino)-1-(trifluoromethyl)[1,2,4]triazolo[4,3-a]quinoxaline). The most potent A2 ligand is 4-amino-8-chloro-1-phenyl[1,2,4]triazolo[4,3-a]quinoxaline. Representatives from this series appear to act as antagonists at both A1 and A2 receptors since they antagonize the inhibiting action of CHA on norepinephrine-stimulated cAMP formation in fat cells and they decrease cAMP accumulation induced by adenosine in limbic forebrain slices. Thus certain members of I are among the most potent and A1 or A2 selective non-xanthine adenosine antagonists known.

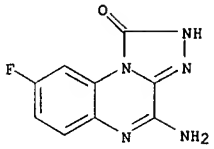
IT **127710-84-3P 127710-85-4P 127710-86-5P**
127710-87-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and adenosine receptor antagonist activity and antidepressant activity of)

RN 127710-84-3 CAPLUS
CN [1,2,4]Triazolo[4,3-a]quinoxalin-1(2H)-one, 4-amino-8-fluoro-, monohydrobromide (9CI) (CA INDEX NAME)

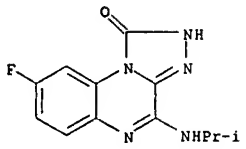


● HBr

RN 127710-85-4 CAPLUS
CN [1,2,4]Triazolo[4,3-a]quinoxalin-1(2H)-one, 4-amino-8-fluoro- (9CI) (CA INDEX NAME)

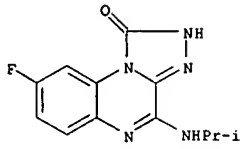


RN 127710-86-5 CAPLUS
CN [1,2,4]Triazolo[4,3-a]quinoxalin-1(2H)-one, 8-fluoro-4-[(1-methylethyl)amino]-, monohydrobromide (9CI) (CA INDEX NAME)



● HBr

RN 127710-87-6 CAPLUS
CN [1,2,4]Triazolo[4,3-a]quinoxalin-1(2H)-one, 8-fluoro-4-[(1-methylethyl)amino]- (9CI) (CA INDEX NAME)



=> LOG HOLD

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	31.48	374.02
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-3.00	-3.00

SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 09:15:11 ON 18 APR 2006

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSSPTA1623ZCT

PASSWORD:
* * * * * * RECONNECTED TO STN INTERNATIONAL * * * * * *
SESSION RESUMED IN FILE 'CAPLUS' AT 09:31:21 ON 18 APR 2006
FILE 'CAPLUS' ENTERED AT 09:31:21 ON 18 APR 2006
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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	31.48	374.02
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-3.00	-3.00

=> FILE MEDLINE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	32.86	375.40
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-3.00	-3.00

FILE 'MEDLINE' ENTERED AT 09:33:03 ON 18 APR 2006

FILE LAST UPDATED: 15 APR 2006 (20060415/UP). FILE COVERS 1950 TO DATE.

On December 11, 2005, the 2006 MeSH terms were loaded.

The MEDLINE reload for 2006 is now (26 Feb.) available. For details on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04 mesh.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05 med data changes.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

OLDMEDLINE is covered back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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             2 GSKS
          1280 GSK
                 (GSK OR GSKS)
         40852 GLYCOGEN
            86 GLYCOGENS
         40864 GLYCOGEN
                 (GLYCOGEN OR GLYCOGENS)
         81338 SYNTHASE
         17576 SYNTHASES
         93098 SYNTHASE
                 (SYNTHASE OR SYNTHASES)
          5130 GLYCOGEN SYNTHASE
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L12       2251 L11 AND INHIB?

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=> S L12 AND REVIEW AND 2002/PY
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MEDLINE SEARCH FOR ENABLEMENT ISSUES (112/1). "STATE OF THE ART"

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L15         12 L13 OR L14

=> D 1-12 IBIB ABS

L15  ANSWER 1 OF 12     MEDLINE on STN
ACCESSION NUMBER:   2003602077     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 14683459
TITLE:              Physiological roles of glycogen synthase
                    kinase-3: potential as a therapeutic target for diabetes
                    and other disorders.
AUTHOR:             Woodgett J R
CORPORATE SOURCE:   Ontario Cancer Institute, 610 University Avenue, Toronto,
                    Ontario M5G 2M9, Canada.. jwoodget@uhnresearch.ca
SOURCE:             Current drug targets. Immune, endocrine and metabolic
                    disorders, (2003 Dec) Vol. 3, No. 4, pp. 281-90.
                    Ref: 113
                    Journal code: 101121150. ISSN: 1568-0088.
PUB. COUNTRY:       Netherlands
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
                    General Review; (REVIEW)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200402
ENTRY DATE:         Entered STN: 20031220
                    Last Updated on STN: 20040219
                    Entered Medline: 20040218
AB  Glycogen synthase kinase-3 (GSK-3) has
    perplexed signal transduction researchers since its detection in skeletal
    muscle 25 years ago. The enzyme confounds most of the rules normally
    associated with protein kinases in that it exhibits significant activity,
    even in resting, unstimulated cells. However, the protein is highly
    regulated and potently inactivated in response to signals such as insulin
    and polypeptide growth factors. The enzyme also displays a distinct and
    unusual preference for substrates that have been previously phosphorylated
    by other protein kinases which provides obvious opportunities for
    cross-talk. Its substrates are diverse and are predominantly regulatory
    molecules. The molecular cloning of the kinase revealed it to be encoded
    by two related but distinct genes. Moreover, the mammalian proteins
    showed remarkable similarity to a fruitfly protein isolated on the basis
    of its role in cell fate determination. From these humble beginnings,
    study of the enzyme has accrued further surprises such as its
    inhibition by lithium, its regulation by serine and tyrosine
    phosphorylation and its implication in several human disorders including
    Alzheimers disease, bipolar disorder, cancer and diabetes. Most recently,
    small molecule inhibitors of GSK-3 have been developed
    and assessed for therapeutic potential in several of models of
    pathophysiology. The question is whether modulation of such an "involved"
    enzyme could lead to selective restoration of defects without multiple
    unwanted side effects. This review summarizes current knowledge
    of GSK-3 with respect to its known functions, together with an
    assessment of its real-life potential as a drug target for chronic
    conditions such as type 2 diabetes.

L15  ANSWER 2 OF 12     MEDLINE on STN
ACCESSION NUMBER:   2003577447     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 14656484
TITLE:              Anti-Mullerian hormone, beta-catenin and Mullerian duct
                    regression.
AUTHOR:             Xavier F; Allard S
CORPORATE SOURCE:   Unite de recherches sur l'Endocrinologie du Developpement,
                    INSERM, 32 rue des Carnets, 93140 Clamart, France..
                    francoise.xavier@inserm.ipsc.u-psud.fr
SOURCE:             Molecular and cellular endocrinology, (2003 Dec 15)
                    Vol. 211, No. 1-2, pp. 115-21. Ref: 53
                    Journal code: 7500844. ISSN: 0303-7207.
PUB. COUNTRY:       Ireland
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
                    General Review; (REVIEW)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200408
ENTRY DATE:         Entered STN: 20031216
                    Last Updated on STN: 20040901
                    Entered Medline: 20040831
AB  The embryo is initially sexually indifferent, and correct sexual
    development is dependent on gonadal hormone production. Thus, in the male
    embryo, anti-Mullerian hormone (AMH), secreted by the Sertoli cells of the
    testis, induces regression of the Mullerian duct, the anlagen of female
    reproductive tract. This hormone causes ductal epithelial regression
    through a paracrine mechanism originating in periductal mesenchyme and the
    cross-talk between the mesenchymal and epithelial layers accounts for the
    cranial-to-caudal pattern of Mullerian regression. Here, we
    review and discuss recent developments concerning the relationship
    of apoptosis of Mullerian duct to tissue remodeling, mesenchymal-
    epithelial interactions, and involvement of beta-catenin in AMH signaling
    in periductal mesenchyme. Determining the role of beta-catenin/LEF-1
    signaling is critical for understanding AMH action during Mullerian duct
    regression.

L15  ANSWER 3 OF 12     MEDLINE on STN
ACCESSION NUMBER:   2003405564     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 12943495
TITLE:              Challenges and opportunities with glycogen
                    synthase kinase-3 inhibitors for insulin
                    resistance and Type 2 diabetes treatment.
AUTHOR:             Eldar-Finkelman Hagit; Ilouz Ronit
CORPORATE SOURCE:   Department of Human Genetics and Molecular Medicine,
                    Sackler School of Medicine, Ramat Aviv, Tel-Aviv
                    University, Israel.. heldar@post.tau.ac.il
SOURCE:             Expert opinion on investigational drugs, (2003 Sep)
                    Vol. 12, No. 9, pp. 1511-9. Ref: 83
                    Journal code: 9434197. ISSN: 1354-3784.
PUB. COUNTRY:       England: United Kingdom
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
                    General Review; (REVIEW)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200401
ENTRY DATE:         Entered STN: 20030829
                    Last Updated on STN: 20040107
                    Entered Medline: 20040106
AB  The role of the serine/threonine protein kinase, glycogen
    synthase kinase-3 (GSK-3), in attenuating the insulin
    signalling pathway has led to the concept that inhibition of
    GSK-3 may have therapeutic benefits in the treatment of insulin
    resistance and Type 2 diabetes. Indeed, various selective GSK-3
    inhibitors have been developed recently and have proven to promote
    insulin-like effects and to act as insulin sensitisers in both in vitro
    and in vivo systems. GSK-3 inhibition may thus
    present a new, effective approach for the treatment of insulin resistance
    and Type 2 diabetes. This review describes the qualifications
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of GSK-3 as a novel drug-discovery target for Type 2 diabetes and discusses the strategies and challenges in developing small-molecule **inhibitors** for this important protein kinase.

L15 ANSWER 4 OF 12 MEDLINE on STN
ACCESSION NUMBER: 2003352236 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12884912
TITLE: The role of integrin-linked kinase (ILK) in cancer progression.
AUTHOR: Persad Sujata; Dedhar Shoukat
CORPORATE SOURCE: Hamilton Regional Cancer Center and McMaster University, Hamilton, Ontario, Canada.
SOURCE: Cancer metastasis reviews, **(2003 Dec)** Vol. 22, No. 4, pp. 375-84. Ref: 53
Journal code: 8605731. ISSN: 0167-7659.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200403
ENTRY DATE: Entered STN: 20030730
Last Updated on STN: 20040327
Entered Medline: 20040326

AB Integrin-linked kinase (ILK) is an intracellular protein, which interacts with the cytoplasmic domains of integrin beta and beta3 subunits. ILK is a 59 kDa protein containing a phosphoinositide phospholipid-binding domain flanked by an N-terminal ankyrin repeat domain and a C-terminal serine/threonine protein kinase domain. Genetic and biochemical evidence have established an essential role of ILK in connecting integrins to the actin cytoskeleton. Apart from integrins, ILK interacts with several adaptor and signaling proteins resulting in its activation and localization to focal adhesion plaques. The kinase activity of ILK is stimulated upon integrin engagement, as well as by growth factors and chemokines in a PI-3Kinase-dependent manner. ILK can mediate the phosphorylation of a variety of intracellular substrates, most notable of which are: protein kinase B (PKB/Akt), **glycogen synthase** kinase-3 (**GSK-3**) and myosin light chain. Gain and loss of function strategies have shown that overexpression, and/or constitutive activation of ILK results in oncogenic transformation and progression to invasive and metastatic phenotypes. In addition ILK expression and activity are upregulated in several types of cancers. In this **review**, we summarize the adaptor and signaling properties ofILK, and also progress in the identification of therapeutic strategies for **inhibition** of ILK activity.

L15 ANSWER 5 OF 12 MEDLINE on STN
ACCESSION NUMBER: 2003208699 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12600273
TITLE: Signalling specificity of Ser/Thr protein kinases through docking-site-mediated interactions.
AUTHOR: Biondi Ricardo M; Nebreda Angel R
CORPORATE SOURCE: Division of Signal Transduction Therapy, School of Life Sciences, University of Dundee, Dundee DD1 5EH, Scotland, U.K.. r.m.biondi@phosphosites.com
SOURCE: The Biochemical journal, **(2003 May 15)** Vol. 372, No. Pt 1, pp. 1-13. Ref: 138
Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030506
Last Updated on STN: 20030704
Entered Medline: 20030703

AB Signal transduction pathways use protein kinases for the modification of protein function by phosphorylation. A major question in the field is how protein kinases achieve the specificity required to regulate multiple cellular functions. Here we **review** recent studies that illuminate the mechanisms used by three families of Ser/Thr protein kinases to achieve substrate specificity. These kinases rely on direct docking interactions with substrates, using sites distinct from the phospho-acceptor sequences. Docking interactions also contribute to the specificity and regulation of protein kinase activities. Mitogen-activated protein kinase (MAPK) family members can associate with and phosphorylate specific substrates by virtue of minor variations in their docking sequences. Interestingly, the same MAPK docking pocket that binds substrates also binds docking sequences of positive and negative MAPK regulators. In the case of **glycogen synthase** kinase 3 (GSK3), the presence of a phosphate-binding site allows docking of previously phosphorylated (primed) substrates; this docking site is also required for the mechanism of GSK3 **inhibition** by phosphorylation. In contrast, non-primed substrates interact with a different region of GSK3. Phosphoinositide-dependent protein kinase-1 (PDK1) contains a hydrophobic pocket that interacts with a hydrophobic motif present in all known substrates, enabling their efficient phosphorylation. Binding of the substrate hydrophobic motifs to the pocket in the kinase domain activates PDK1 and other members of the AGC family of protein kinases. Finally, the analysis of protein kinase structures indicates that the sites used for docking substrates can also bind N- and C-terminal extensions to the kinase catalytic core and participate in the regulation of its activity.

L15 ANSWER 6 OF 12 MEDLINE on STN
ACCESSION NUMBER: 2003065113 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12575817
TITLE: Neuronal survival and cell death signaling pathways.
AUTHOR: Morrison Richard S; Kinoshita Yoshito; Johnson Mark D; Ghatan Saadi; Ho Joseph T; Garden Gwenn
CORPORATE SOURCE: Department of Neurological Surgery, University of Washington School of Medicine, Box 356470, Seattle, Washington 98195-6470, USA.
SOURCE: Advances in experimental medicine and biology, **(2002)** Vol. 513, pp. 41-86. Ref: 394
Journal code: 0121103. ISSN: 0065-2598.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030211
Last Updated on STN: 20030716
Entered Medline: 20030715

AB Neuronal viability is maintained through a complex interacting network of signaling pathways that can be perturbed in response to a multitude of cellular stresses. A shift in the balance of signaling pathways after stress or in response to pathology can have drastic consequences for the function or the fate of a neuron. There is significant evidence that acutely injured and degenerating neurons may die by an active mechanism of cell death. This process involves the activation of discrete signaling pathways that ultimately compromise mitochondrial structure, energy metabolism and nuclear integrity. In this **review** we examine recent evidence pertaining to the presence and activation of anti- and pro-cell death regulatory pathways in nervous system injury and degeneration.

L15 ANSWER 7 OF 12 MEDLINE on STN

ACCESSION NUMBER: 2002616964 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12374432
TITLE: The Wnt signaling pathway in bipolar disorder.
AUTHOR: Gould Todd D; Manji Husseini K
SOURCE: The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry, **(2002 Oct)** Vol. 8, No. 5, pp. 497-511. Ref: 143
Journal code: 9504819. ISSN: 1073-8584.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20021011
Last Updated on STN: 20030305
Entered Medline: 20030304

AB The Wnt signaling pathway is a highly conserved pathway critical for proper embryonic development. However, recent evidence suggests that this pathway and one of its key enzymes, **glycogen synthase** kinase 3beta, may play important roles in regulating synaptic plasticity, cell survival, and circadian rhythms in the mature CNS-all of which have been implicated in the pathophysiology and treatment of bipolar disorder. Furthermore, two structurally highly dissimilar medications used to treat bipolar disorder, lithium and valproic acid, exert effects on components of the Wnt signaling pathway. Together, these data suggest that the Wnt signaling pathway may play an important role in the treatment of bipolar disorder. Here, the authors **review** the modulation of the Wnt/ **GSK**-3beta signaling pathway by mood-stabilizing agents, focusing on two therapeutically relevant aspects: neuroprotection and modulation of circadian rhythms. The future development of selective **GSK** -3beta **inhibitors** may have considerable utility not only for the treatment of bipolar disorder but also for a variety of classical neurodegenerative disorders.

L15 ANSWER 8 OF 12 MEDLINE on STN
ACCESSION NUMBER: 2002417415 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12171564
TITLE: Prospects for kinase activity modulators in the treatment of diabetes and diabetic complications.
AUTHOR: Bullock William H; Magnuson Steven R; Choi Soongyu; Gunn David E; Rudolph Joachim
CORPORATE SOURCE: Bayer Research Center, 400 Morgan Lane, West Haven, CT, 06516-4175, USA.. william.bullock.b@bayer.com
SOURCE: Current topics in medicinal chemistry, **(2002 Sep)** Vol. 2, No. 9, pp. 915-38. Ref: 251
Journal code: 101119673. ISSN: 1568-0266.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20020813
Last Updated on STN: 20030117
Entered Medline: 20030116

AB The worldwide population afflicted with diabetes is growing at an epidemic rate. There are almost five times the number of people suffering from this disease today as compared to 10 years ago and the worldwide diabetic population is expected to exceed 300 million by the year 2028. This trend appears to be driven by the world's adoption of a "western lifestyle" comprising a combination of unhealthy dietary habits and a sedentary daily routine. Today, diabetes is the sixth leading cause of death in the United States and the death rates associated with diabetes have increased by 30% over the last decade. While medications are available to reduce blood glucose, approximately one third of the patients on oral medications will eventually fail to respond and require insulin injections. Consequently, there is a tremendous medical need for improved medications to manage this disease that demonstrate superior efficacy. Emerging knowledge regarding the underlying mechanisms that impair glucose-stimulated insulin secretion and the action of insulin on its target tissues has grown tremendously over the last two decades. During that same period of time, an understanding of the important role that phosphorylation state plays in signal transduction has drawn attention to several kinases as attractive approaches for the treatment of diabetes. Recent advances include the discovery of a"small molecule" allosteric binding site on the insulin receptor, **inhibitors** of **glycogen synthase** kinase-3(**GSK**-3) which improve insulin sensitivity in diabetic animal models and **inhibitors** of protein kinase C- beta that are presently being evaluated in clinical trials for diabetic retinopathy. This **review** will detail these recent discoveries and highlight emerging biological targets that hold potential to normalize blood glucose and prevent the progression of diabetes related complications.

L15 ANSWER 9 OF 12 MEDLINE on STN
ACCESSION NUMBER: 2002361857 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12111750
TITLE: **Glycogen synthase** kinase 3 (**GSK** -3) **inhibitors** as new promising drugs for diabetes, neurodegeneration, cancer, and inflammation.
AUTHOR: Martinez Ana; Castro Ana; Dorronsoro Isabel; Alonso Mercedes
CORPORATE SOURCE: Instituto de Quimica Medica (CSIC), Juan de la Cierva 3, 28006 Madrid, Spain.. iqmam06@pinar2.csic.es
SOURCE: Medicinal research reviews, **(2002 Jul)** Vol. 22, No. 4, pp. 373-84. Ref: 81
Journal code: 8103150. ISSN: 0198-6325.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020712
Last Updated on STN: 20021218
Entered Medline: 20020730

AB **Glycogen synthase** kinase 3 (**GSK**-3) was initially described as a key enzyme involved in glycogen metabolism, but is now known to regulate a diverse array of cell functions. Two forms of the enzyme, **GSK**-3alpha and **GSK**-3beta, have been previously identified. Small molecules **inhibitors** of **GSK**-3 may, therefore, have several therapeutic uses, including the treatment of neurodegenerative diseases, diabetes type II, bipolar disorders, stroke, cancer, and chronic inflammatory disease. As there is lot of recent literature dealing with the involvement of **GSK**-3 in the molecular pathways of different diseases, this **review** is mainly focused on the new **GSK**-3 **inhibitors** discovered or specifically developed for this enzyme, their chemical structure, synthesis, and structure-activity relationships, with the aim to provide some clues for the future optimization of these promising drugs.

L15 ANSWER 10 OF 12 MEDLINE on STN
ACCESSION NUMBER: 2002298810 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12039794
TITLE: **Glycogen synthase** kinase-3beta: a novel regulator of cardiac hypertrophy and development.
AUTHOR: Hardt Stefan E; Sadoshima Junichi
CORPORATE SOURCE: Department of Cell Biology and Molecular Medicine,

Department of Medicine, Cardiovascular Research Institute, UMDNJ, New Jersey Medical School, Newark.
SOURCE: Circulation research, **(2002 May 31)** Vol. 90, No. 10, pp. 1055-63. Ref: 136
Journal code: 0047103. E-ISSN: 1524-4571.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020602
Last Updated on STN: 20021218
Entered Medline: 20020607

AB **Glycogen synthase** kinase-3beta (**GSK**-3beta) is a ubiquitously expressed constitutively active serine/threonine kinase that phosphorylates cellular substrates and thereby regulates a wide variety of cellular functions, including development, metabolism, gene transcription, protein translation, cytoskeletal organization, cell cycle regulation, and apoptosis. The activity of **GSK**-3beta is negatively regulated by protein kinase B/Akt and by the Wnt signaling pathway. Increasing lines of evidence show that **GSK**-3beta is an essential negative regulator of cardiac hypertrophy and that the **inhibition** of **GSK**-3beta by hypertrophic stimuli is an important mechanism contributing to the development of cardiac hypertrophy. **GSK**-3beta also plays an important role in regulating cardiac development. In this **review**, the role of **GSK**-3beta in cardiac hypertrophy and development and the potential underlying mechanisms are discussed.

L15 ANSWER 11 OF 12 MEDLINE on STN
ACCESSION NUMBER: 2002151659 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11883528
TITLE: Role of **glycogen synthase** kinase-3 in cancer: regulation by Wnts and other signaling pathways.
AUTHOR: Manoukian Armen S; Woodgett James R
CORPORATE SOURCE: Division of Experimental Therapeutics, Ontario Cancer Institute Toronto, Canada.
SOURCE: Advances in cancer research, **(2002)** Vol. 84, pp. 203-29. Ref: 150
Journal code: 0370416. ISSN: 0065-230X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020311
Last Updated on STN: 20021218
Entered Medline: 20020826

AB Although **glycogen synthase** kinase-3 (**GSK**-3) is but one of more than a thousand distinct serine/threonine kinases present in the mammalian genome, this enzyme has attracted attention for its role in a diverse range of cellular processes and its positioning at a nexus of several signaling pathways that are important in cancer and other human diseases. The association of **GSK**-3 with widely different functions, from glycogen metabolism to fruit fly segmentation and slime mold differentiation, was initially perplexing. However, as the context of the biological processes involving this enzyme has been clarified, unifying themes have emerged that begin to explain its pleiotropic nature. Unlike most protein kinases involved in signaling, **GSK**-3 is active in unstimulated, resting cells. Its activity is inactivated during cellular responses and its substrates therefore tend to be dephosphorylated. As more of these targets have been identified and the effects of their modification by **GSK**-3 determined, most have been found to be functionally **inhibited** by **GSK**-3. Hence, this kinase appears to act as a general repressor, keeping its targets switched off or inaccessible under resting conditions. The rarity of this form of regulation is perhaps related to the diversity of its targets. Over the past decade, the importance of **GSK**-3 has been established by three significant properties: its remarkable evolutionary conservation, allowing analysis in genetically tractable organisms; its involvement in the Wnt/wingless signaling pathway; and its **inhibition** by agonists of the prosurvival phosphatidylinositol 3' kinase (PI3'K) pathway. This **review** covers recent advances in understanding the physiological roles of this enzyme, particularly in the context of cancer.

L15 ANSWER 12 OF 12 MEDLINE on STN
ACCESSION NUMBER: 2002124710 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11839557
TITLE: Beta-catenin--a linchpin in colorectal carcinogenesis?.
AUTHOR: Wong Newton Alexander Chiang Shuek; Pignatelli Massimo
CORPORATE SOURCE: Department of Pathology, University of Edinburgh, Edinburgh, Scotland, United Kingdom.
SOURCE: The American journal of pathology, **(2002 Feb)** Vol. 160, No. 2, pp. 389-401. Ref: 140
Journal code: 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020226
Last Updated on STN: 20021218
Entered Medline: 20020319

AB An important role for beta-catenin pathways in colorectal carcinogenesis was first suggested by the protein's association with adenomatous polyposis coli (APC) protein, and by evidence of dysregulation of beta-catenin protein expression at all stages of the adenoma-carcinoma sequence. Recent studies have, however, shown that yet more components of colorectal carcinogenesis are linked to beta-catenin pathways. Pro-oncogenic factors that also release beta-catenin from the adherens complex and/or encourage translocation to the nucleus include ras, epidermal growth factor (EGF), c-erbB-2, PKC-betaII, MUC1, and PPAR-gamma, whereas anti-oncogenic factors that also **inhibit** nuclear beta-catenin signaling include transforming growth factor (TGF)-beta, retinoic acid, and vitamin D. Association of nuclear beta-catenin with the T cell factor (TCF)/lymphoid enhancer factor (LEF) family of transcription factors promotes the expression of several compounds that have important roles in the development and progression of colorectal carcinoma, namely: c-myc, cyclin D1, gastrin, cyclooxygenase (COX)-2, matrix metalloproteinase (MMP)-7, urokinase-type plasminogen activator receptor (aPAR), CD44 proteins, and P-glycoprotein. Finally, genetic aberrations of several components of the beta-catenin pathways, eg, Frizzled (Frz), AXIN, and TCF-4, may potentially contribute to colorectal carcinogenesis. In discussing the above interactions, this **review** demonstrates that beta-catenin represents a key molecule in the development of colorectal carcinoma.

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